REMARKS

Claims 1-3 and 6-14 were pending before the Office. Claims 1 and 14 are hereby amended. Claims 6-8 are withdrawn. Accordingly, claims 1-3 and 6-14 will be pending upon entry of this paper.

No new matter is added by this amendment.

The amendments are made solely to claim more fully the invention and/or to expedite prosecution of the present application and should in no way be construed as an acquiescence to any of the Examiner's suggestions regarding prior art in the Office Action issued in the present application. Applicants reserve the right to pursue the subject matter of the claims as originally filed or similar claims in one or more subsequent applications.

Support for the amendments can be found throughout the originally-filed application, including the specification, drawings, examples and claims.

The rejection under 35 U.S.C. 102(e) is overcome

The Office Action rejects claims 1, 2 and 14 under 35 U.S.C. 102(e) as allegedly being anticipated by U.S. Published Application No. 2004-0009126 A1 to Pilkiewicz et al. ("PILKIEWICZ"). More in particular, the Examiner contends that PILKIEWICZ teaches "a method of treating [a] bacterial lung infection comprising local administration of ciprofloxacin by inhalation, wherein the ciprofloxacin is in the form of a particle and may be in the form of dry powder." Applicants respectfully disagree with the rejection and the Examiner's characterization of the reference and traverse as follows.

M.P.E.P § 2131 states that "[a] claim is anticipated **only if each and every element** as set forth in the claim is found, either expressly or inherently described, in a single prior

art reference." *See Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987) (emphasis added). Moreover, the prior art must contain an enabling disclosure for a Section 102 rejection to stand. *See Chester v. Miller*, 15 U.S.P.Q.2d 1333, 1336 (Fed. Cir. 1990). "A claimed reference cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 (Fed. Cir. 2003). A reference contains an enabling disclosure if a person of ordinary skill in the art could have combined the description of the invention in the prior art reference with his own knowledge of the art to have placed himself in possession of the invention. *See, e.g. Id.* At 1354 and *In re Donohue,* 226 U.S.P.Q. 619, 621 (Fed. Cir. 1985).

Respectfully, the following explanation will show that PILKIEWICZ does not teach, either expressly or inherently, each and every element of the presently claimed invention. Moreover, PILKIEWICZ does not contain an enabling disclosure sufficient to have placed a person of ordinary skill in possession of the invention. Accordingly, Applicants request reconsideration and withdrawal of the Section 102 rejection.

Claim 1, as presently amended, recites a method for controlling bacterial diseases of the respiratory organs in humans and animals by local administration of an antibacterially effective amount of solid betaine of formula (III) (ciprofloxacin or enrofloxacin in betaine form) or its solid slightly soluble salt, wherein R = H (ciprofloxicin), C_2H_5 (enrofloxacin) and, wherein the solid betaine is administered in a powder form or powder-containing suspension. The present application states "[i]t has been found, surprisingly, that control of diseases of the respiratory organs, especially lung diseases caused by bacteria, is extremely

successful when ciprofloxacin or enrofloxacin is administered locally as solid betaine and/or as solid slightly soluble betaine salt. The active ingredient concentration in the lungs can be kept for a lengthy period at a level desirable from the medical viewpoint for optimal treatment. Besides the higher and long-lasting active ingredient level at the site of the infection, it is possible to achieve simultaneously a comparatively low systemic concentration of the active ingredient, so that side effects of the medication and the disquieting development of resistance through systemic selection pressure are at least drastically reduced or even entirely prevented in this way." The application also demonstrates in the Examples that the intratracheal use of ciprofloxacin betaine provides a significant improvement of the use of equal dosages of ciprofloxacin hydrochloride (the conventional form of ciprofloxacin) in the clearing of microorganisms from the lungs of test rats. See page 8-9. In addition, the Examples demonstrate that intratracheal administration of ciprofloxacin-betaine provides significantly improved kinetic parameters (e.g., AUC, C_{max}) over the conventional ciprofloxacin-hydrocholoride. See page 8.

PILKIEWICZ neither expressly nor inherently teaches or suggests each and every element of the claims, in particular, the specific use of ciprofloxacin betaine or the use of a dry powder of ciprofloxacin betain. While PILKIEWICZ relates generally to inhalation forms of antiinfective agents, it fails to teach or suggest the present invention. First, PILKIEWICZ does not at any point specifically teach the administration via any route—e.g., intratracheal or intravenous—of the betaine form of ciprofloxacin. Only the present inventors, not PILKIEWICZ, have recognized the surprising finding that the solid betaine form of ciprofloxacin can be successfully and effectively administered intratracheally in a

powder or powder-containing suspension.

Moreover, PILKIEWICZ should not be considered proper prior art under Section 102 because the reference is not sufficiently enabled to make and/or use the present invention as presently claimed. First, PILKEIWICZ does not specifically teach, suggest or even recognize the specific advantages of administering the betaine form of ciprofloxacin. One of ordinary skill in the art would not have combined the teachings of the reference with their own knowledge to reach the present invention because their own knowledge would have only reflected that which was conventional in the art—namely, the use of ciprofloxacin dihydrochloride. Moreover, PILKEIWICZ appears only to suggest the use of lipid-based compositions. In fact, PILKEIWICZ stresses the purported disadvantages of administering solid form antiinfective agents by inhalation—including susceptibility to chemical and enzymatic in vivo degradation and rapid clearance problems. See paragraph 6. The vast remainder of the specification is focused on the making and using of liposomal formulations of antiinfective agents for administration by inhalation, which are purported to overcome the deficiencies of dry powder formulations of the art. Indeed, the references teaches and shows in Figure 2 that the intratracheally-delivered liposomal ciprofloxacin formulation of PILKEIWICZ overcomes the drug retention problem characterized by free ciprofloxacin delivered intratracheally. See paragraphs 59 and 74. Accordingly, PILKEIWICZ does not enable the present invention.

Because PILKEIWICZ neither teaches nor suggests each and every element of the presently claimed invention, nor does it sufficiently enable the present invention, the rejection cannot stand under Section 102(e). Accordingly, Applicants respectfully request

reconsideration and withdrawal of the rejection.

The rejections under 35 U.S.C. § 103 are overcome

The Examiner has rejected claims 1, 2 and 14 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Mayer et al. ("Clinical presentation of inhalational anthrax following bioterrorism exposure," Journal of the American Medical Association, November 28, 2001, Vol. 286, No. 20, pp. 2549-2553) ("MAYER") in view of Li et al. ("Ciprofloxacin-loaded bovine serum albumin microspheres: preparation and drug-release in vitro," J. Microencapsulation, 2001, Vol. 19, No. 6, pp. 825-829) ("LI"). In addition, the Examiner has rejected claims 3 and 9-13 under 35 U.S.C. § 103(a) as allegedly being unpatentable over MAYER in view of LI and in further view of Grohe et al. (U.S. Patent No. 4,670,444) ("GROHE") and Vetter et al. (U.S. Patent No. 5,808,076 ("VETTER").

More in particular, the Examiner argues that the skilled artisan would have been motivated to modify MAYER, which relates to the intravenous administration of ciprofloxacin to anthrax lung infection patients, with the teachings of LI, which purportedly relates to the administration of ciprofloxacin by inhalation. The Examiner argues that the skilled artisan would have been motivated to make such a modification because, as noted in the Office Action, LI teaches that intravenous or oral administration of ciprofloxacin has "relatively unfavorable pharmacokinetic profile in the lower respiratory track."

Applicants respectfully disagree with the rejections and traverse as follows. For the reasons set forth below, neither MAYER nor LI, either taken alone or in combination, would have led one of ordinary skill in the art to make or use the instantly claimed invention. Neither GROHE nor VETTER cure the deficiencies of MAYER or LI.

As mentioned above, the present inventors have invented a new, useful and nonobvious method for controlling bacterial diseases of the respiratory organs in humans and animals by local administration of an antibacterially effective amount of solid betaine of formula (III) (ciprofloxacin or enrofloxacin in betaine form) or its solid slightly soluble salt, wherein R = H (ciprofloxicin), C_2H_5 (enrofloxacin) and, wherein the solid betaine is administered in a powder form or powder-containing suspension. The invention is based on the surprising discovery that control of diseases of the respiratory organs, especially lung diseases caused by bacteria, is extremely successful when ciprofloxacin or enrofloxacin is administered locally as solid betaine and/or as solid slightly soluble betaine salt.

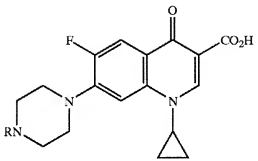
Turning to the references, MAYER relates to a report on the diagnosis and treatment of two rare cases of inhalation anthrax using a tri-therapy regimen of ciprofloxicin at 400 mg every 8 hours, rifampin at 300 mg every 12 hours, and clindamycin at 900 mg every 8 hours, each administered intravenously. MAYER does not specifically teach the use of a solid betaine form of ciprofloxicin or the administration of same via an inhalation route. LI relates to a study reporting on the preparation and physical characterization (e.g., release rate of drug) of ciprofloxacin-encapsulated microspheres for use in dry powder inhalers. In contrast with the invention, LI does not teach or suggest the specific use of the betaine form of ciprofloxacin or enrofloxacin, or a method of local administration of a solid betaine form of ciprofloxacin or enrofloxacin to control a bacterial disease, as is required by the present invention. LI instead relates to the preparation and characterization of ciprofloxacin microparticles and lacks any teaching or showing that its microparticles would even be effective in a method for controlling bacterial disease, as is required by the present

invention. Thus, neither MAYER nor LI, either taken alone or in combination, teach or even fairly suggest the present invention.

That the prior art references neither teach nor suggest the use of the betaine form of ciprofloxacin or enrofloxacin is significant. As pointed out in the present application, "ciprofloxacin hydrochloride and enrofloxacin hydrochloride are antibacterial quinolonecarboxylic acid derivatives which have been known for about 20 years and which can be employed extremely successfully both for the prophylaxis and for the treatment of systemic and local bacterial infections." See page 2 of the application. The present inventor surprisingly discovered that, while the prior art uses various dosage formulations (e.g., tablets, capsules, pills, suspensions, pastes and sprays), "control of diseases of the respiratory organs, especially lung diseases caused by bacteria, is extremely successful when ciprofloxacin or enrofloxacin is administered locally as solid betaine and/or as solid slightly soluble betaine salt." See page 2-3. Given that ciprofloxacin has been known for 20 years, that no one else previously has conceived of the method of the invention, which specifically involves the local administration of the betaine form of ciprofloxacin or enrofloxacin, is evidence of a long-felt but unsolved need which was first provided by the present inventors.

Neither GROHE nor VETTER cure the deficiencies of either MAYER or LI. GROHE and VETTER are relied on by the Examiner for the elements of dependent claim 3 and 9-13, which are directed to particular salts of the compounds used in the base claim methods. Neither GROHE nor VETTER, either alone or in combination, teach or suggest the recited steps of the claimed invention, namely a method for controlling bacterial diseases

of the respiratory organs in humans and animals by local administration of an antibacterially effective amount of solid betaine of the formula (III)



wherein R = H, C_2H_5 or its solid slightly soluble salt, wherein the solid betaine is administered in a powder form or powder-containing suspension. Instead, each of GROHE and VETTER relate merely to preparing salt variations of ciprofloxacin.

Accordingly, a conclusion of obviousness simply cannot stand in view of the above remarks. Moreover, the rejection is improper in view of the U.S. Supreme Court's and the USPTO's current interpretation of obviousness under 35 U.S.C. § 103, and in further view of various secondary factors discussed below, including long-felt but unmet need of the invention.

The USPTO has issued Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 ("Guidelines") in view of the Supreme Court's recent decision in KSR International Co. v. Teleflex Inc., 550 U.S. __, 82 USPQ2d 1385 (2007). The Guidelines were published in the Fed. Reg., Vol. 72, no. 195, October 10, 2007, now incorporated at MPEP § 2141 of the Eight Edition, Incorporating Revision No. 6. As pointed out in the Guidelines, the Supreme Court in KSR reaffirmed the analytical framework for determining obviousness as set forth in Graham v. John Deere Co., 338 U.S. 1, 148 USPQ 459 (1966),

and also held that the Federal Circuit's application of its teaching-suggestion-motivation test was too formalistic, while still permissible as one of several rationales supporting an obviousness rejection.

Under Graham, obviousness is a question of law based on underlying factual inquiries that address (1) the scope and content of the prior art, (2) the differences between the claimed invention and the prior art, and (3) the level of ordinary skill in the pertinent art. Consideration must also be given to secondary factors, such as, for example, evidence of commercial success, long felt but unsolved needs, failure of others, and unexpected results. The Supreme Court stated in KSR that "[w]hile the sequence of these questions might be reordered in any particular case, the [Graham] factors continue to define the inquiry that controls." The Guidelines go on to state that "Once the *Graham* factual inquiries are resolved, Office personnel must determine whether the claimed invention would have been obvious to one or ordinary skill in the art."

The Guidelines proceed to articulate seven independent rationales on which a properly made conclusion of obviousness under 35 U.S.C. § 103 may be made: (1) combining prior art elements according to known methods to yield **predictable results**, (2) substitution of one known element for another to obtain **predictable results**, (3) use of known techniques to improve similar devices, methods or products in the same way, i.e., to obtain **predictable results**, (4) applying a known technique to a known device, method or product ready for improvement to yield **predictable results**, (5) choosing from a finite number of identified, **predictable solutions**, with a reasonable expectation of success, i.e., obvious to try, (6) evidence of design incentives or other market forces sufficient to prompt

skilled artisan to vary prior art in a **predictable manner** to result in claimed invention, and (7) evidence of some teaching, suggestion, or motivation in the prior art that would have led the skilled artisan to modify or combine prior art to arrive at claimed invention, i.e., **predictable** modification. All of these tests have or suggest the requirement of **predictability**, which is lacking in the present case. Thus, no rationale can suitably be applied to support a conclusion of obviousness in the present case. More specifically, as the rejection is based on the "obvious to try" rationale, Applicant asserts, as further explained below, that obviousness cannot be concluded based on an "obvious to try" rationale because the invention was not achieved by choosing among a finite number of identified, predictable solutions, with a reasonable chance of success.

The fact that ciprofloxacin has been known for 20 years, as noted above, and has not yet before been developed as a betaine for local delivery in solid form for controlling bacterial diseases should be considered as persuasive secondary evidence that none of the prior art cited would suggest that the invention was predictable or obvious.

For at least the reasons above, the Examiner's conclusion of obviousness cannot stand in view of the U.S. Supreme Court's and the USPTO's current interpretation of obviousness under 35 U.S.C. § 103, and in further view of the secondary factors discussed above. Indeed, other than impermissible hindsight, there is no convincing rationale for combining the cited prior art to achieve the presently claimed method that would support a conclusion of obviousness. Moreover, none of the cited references, considered alone or in

any combination, in fact, teach the recited steps of the method of the invention as presently claimed.

Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 103.

CONCLUSION

In view of the remarks made herein, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. Please charge any required fee or credit any overpayment to Deposit Account No. 04-1105.

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Respectfully submitted,

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